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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/820,420	03/29/2001	Herbert B. Slade	55507USA002	5602

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EXAMINER
HUI, SAN MING R

ART UNIT	PAPER NUMBER
1617	16

DATE MAILED: 08/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/820,420	Applicant(s) SLADE, HERBERT B.	
	Examiner San-ming Hui	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 14-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 14-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Applicant's amendments filed May 28, 2003 have been entered.

The cancellation of claims 11-13 and 24-26 is acknowledged.

Claims 1-10 and 14-23 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds disclosed in the instant specification page 3, line 32 to page 4, line 4, does not reasonably provide enablement for other imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines, and 1,2-bridged imidazoquinoline amines. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In the instant case, the specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required

undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that define "imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines, and 1,2-bridged imidazoquinoline amines" suitable for use in the instant invention other than functionally define these compounds as immune response modifier compound. Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, only a limited number of "imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines, and 1,2-bridged

imidazoquinoline amines" compounds examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. Note also that no physical chemical properties of these compounds are disclosed in the specification. No guidance as to how to select these compounds suitable for practicing the instant invention. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on **all** "imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines, and 1,2-bridged imidazoquinoline amines" compounds necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

Claims 14-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the instant case, the claims are drawn to the method of preventing dermonecrosis by employing the herein claimed compounds to the site of the venom induced immune dysregulation. The breadth of the claim is broad since it encompasses envenomation result from any and every organisms in the world. As for the state of the art, it is known in the pharmaceutical art that absolute prevention of any

medical condition is highly unlikely and highly unpredictable. Working examples of how and when to prevent dermonecrosis are not set forth in the specification. Absent such exemplication, the skilled artisan could not establish the identity of those situations wherein prevention of dermonecrosis would be effected since it is known that systemic reactions to envenomation may occur before the development of the necrotic ulcer, which makes the correct diagnosis difficult (See reference C1 from IDS received January 10, 2003, page 726, col. 1, last paragraph). In other words, it is very difficult to one of skilled artisan to determine whether the patient is suffering from envenomation or not because the systemic reactions, which mimics various different diseases unrelated to the envenomation, usually come before the dermonecrosis. The lack of guidance in the instant specification as to when to administer the herein claimed compounds for the preventing dermonecrosis from happening will require one of skilled artisan to perform undue experimentation in order to practice the herein claimed invention. Furthermore, it is unclear as to the degree of prevention (e.g., total prevention, some prevention, probable prevention, total prevention in most cases...etc.) herein because the specification does not disclose the extent of prevention achieved. Absent such information, one of skilled in the art would have to perform undue experimentation in order to practice the prevention method as herein claimed.

Examiner considers the term "prevention" as for "the treatment or inhibition" and made the following rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10 and 14-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomai et al. (WO 98/17279) and Gerster et al. (US Patent 6,110,929) in view of Bitterman-Deutsch et al. (HAREFUAH, 1990; 119(5-6):137-139), Merigian and Blaho (Reference C1 from IDS received January 10, 2003), and Binder (Medical Toxicology and Adverse Drug Experience, 1989;4(3):163-173), references of record in the previous office action mailed January 2, 2002.

Tomai et al. teaches imidazoquinoline amine compounds including 4-amino-2-ethoxymethyl-α,α -dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol and 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine, preferred compounds herein, can inhibit T-cell Type-2 activities (See particularly the abstract,page 2, line 5-20, page 12, line 13-20, clam 17). By inhibiting the activities of T-cell Type 2, it can also reduce the production of cytokines such as interleukin-3, interleukin-4, and interleukin-5, and the production of IgE and esinophils activities thereby (See particularly the abstract, page 2, line 5-20, page 12, line 13-20, clam 17). Tomai et al. also teaches that IgE is the important component of allergic reaction (See particularly page 12, line 13-20). Tomai et al. also teaches that the imidazoquinoline amine compounds including 4-amino-2-

ethoxymethyl- α,α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol may be administered via topical route as topical cream or gel (See particularly page 3, line 14-15).

Gerster et al. teaches thiazoquinoline compounds including 2-methylthiazolo[4,5-c]quinolin-4-amine, 2-ethylthiazolo[4,5-c]quinolin-4-amine, 2-propylthiazolo[4,5-c]quinolin-4-amine, and 2-butylthiazolo[4,5-c]quinolin-4-amine, preferred compounds herein, can inhibit T-cell Type-2 activities and be useful in wound treatment, inflammation and pain (See particularly the abstract; col. 1, line 43-44, col.6, line 41-46; also also col. 14, ine 63-64). Gerster et al. also teaches that the thiazoquinoline compounds may be formulated into topical creams and ointments (See col. 13, line 49).

The references do not expressly teach the imidazoquinoline and thiazoquinoline compounds are useful in treating and/or preventing dermal lesions by venom induced immune dysregulation caused by spider.

Bitterman-Deutsch et al. teaches that lesions caused by brown recluse spider envenomation may be treated by dapsone, which presumably acting by reducing the activity of polymorphonuclear leukocytes (PMN) (See particularly abstract).

Merigian and Blaho teaches that brown recluse spider envenomation could leads to PMN accumulation (See page 726, col. 1, second paragraph). Merigian and Blaho teaches the local bite area is often filled with inflammatory infiltration with neutrophils and eosinophils (See page 726, col. 2, fourth paragraph).

Binder teaches that local treatment of Black widow spider envenomations includes local wound care (See particularly abstract). Binder also teaches that Black

widow spider envenomation could cause cell membrane lyses and the release of chemotaxis (See the abstract).

It would have been obvious to one skill in the art when the invention was made to employ the imidazoquinoline and thiazoquinoline compounds herein in a method of treating and preventing dermal lesions by venom induced immune dysregulation, in particular caused by spider.

One of ordinary skill in the art would have motivated to employ the imidazoquinoline and thiazoquinoline compounds herein in a method of treating and preventing dermal lesions by venom induced immune dysregulation, in particular caused by spider. The imidazoquinoline and thiazoquinoline compounds herein are known to be useful in treating diseases by T-cell type 2 inhibition, esinophils (polymorphhnuclear leukocyte) inhibition, and IgE inhibition. Therefore, employing the imidazoquinoline and thiazoquinoline compounds herein to treat or prevent dermal lesions caused by brown recluse spider or black widow spider envenomation would be reasonably expected to be effective since blocking polymorphhnuclear leukocyte activities (for example, dapsone) and chemotaxis is an effective treatment module for the spider envenomation, regardless of the underlying mechanism of action of how the dermal lesions developed.

Response to Arguments

Applicant's arguments filed May 28, 2003 averring the instant claims not claiming "absolute prevention" have been fully considered but they are not persuasive. Examiner

notes that Applicant actually considers the term "prevention" is construed as "any degrees of impeding, retarding, or obstructing" (See applicant's response page 7, lines 9-10), which would include 100%, or absolute impeding, retarding, or obstructing. Therefore, the rejection under 35 USC 112, first paragraph is seen to be proper.

Applicant's rebuttal arguments filed May 28, 2003 with regard to the teachings of Wasserman and Anderson that the venom-induced dermonecrotic process is independent of serum or tissue factors and therefore, no motivations are provided by the teachings of the cited prior art to employ the herein claimed compounds to treat venom-induced dermonecrosis have been considered, but are not found persuasive. Firstly, it is not the basis of the rejection to employ the herein claimed to directly against the necrosis induced by the venom. Rather, the collective teachings of the cited prior art would suggest employing the herein claimed compounds to inhibit esinophils (polymorphhnuclear leukocyte) in order to treat the necrosis. Moreover, examiner notes that Wasserman and Anderson teaches the recruitment of PMN occurs at the site of necrosis and the PMN accumulation is essential for the subsequent development of edema, hemorrhage and necrosis at the bite site (See Wasserman and Anderson, page 456-457).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
Patent examiner
Art Unit 1617
August 5, 2003